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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/589,395	06/07/00	ASHKENAZI	A P1759R1

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GENENTECH INC
ATTN DIANE L MARSCHANG
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080

EXAMINER	
NICKOL,G	
ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/589,395	Applicant(s) ASHKENAZI ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-13 and 19-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-13 and 19-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-5 and 14-18 were cancelled. Claims 19-43 were added. Claims 6,10-13, and 19-43 are pending and are currently under consideration.

Information Disclosure Statement

The IDS filed 12-26-00, Paper No. 2 could not be considered because the references were not available to the Examiner. An "in-house" search of these references was submitted- but to date- these references have NOT been found. The Office apologizes for the inconvenience placed on applicant.

Specification

The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the priority status of the present application, for example:

This application claims benefit to provisional application 60/138,240 filed June 9, 1999, now abandoned.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "said agonistic anti-Apo-2 ligand receptor antibody" in Claim 6. There is insufficient antecedent basis for this limitation in the claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 19, 25-26, 28, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, and 13-14 of U.S.

Patent No. 6,252,050 in view of Rougier *et al.* (Semin.Oncol, 1996, Vol. 23, Abstract only) because the present claims are drawn to an obvious variation over the patented claims. Claims 1-11,13-14 of US 6,252,050 are drawn to a method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of an agonistic antibody (see claim 6), which binds to Apo-2 polypeptide or DR4. The instant claims are drawn to the same invention except they further include adding CPT-11 (i.e. a topoisomerase class I inhibitor). Although the conflicting claims are not identical, they are not patentably distinct from each other because it is well known in the art to combine two compositions each of which is taught by prior art to be useful for the same purpose (in this case- treating cancer) in order to form a third composition that is to be used for the very same purpose.

Since Rougier *et al.* teach the clinical efficacy of CPT-11 in treating mammalian cancer, a person of ordinary skill in the art would conclude that the invention defined in the claims in issue is an obvious variation of the invention claimed in the patent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-13, 19-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,252,050, June 12, 1998 in view of Rougier *et al.* (Semin.Oncol, 1996, Vol. 23, Abstract only).

1. US Patent No. 6,252,050 teaches a method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of agonistic anti-DR5 receptor antibody (column 3, lines 34-38) (The DR5 polypeptide is also known as Apo-2- see page 6 of the specification.) wherein said anti-DR5 receptor antibody is monoclonal, wherein said monoclonal comprises a chimeric antibody or human antibody (columns 4-5); wherein said antibody is an antibody which cross reacts with more than one Apo-2 ligand receptor (column 3, lines 11-16); wherein said method further comprises exposing said cancer cells to one or more growth inhibitory substances or radiation (column 25, lines 42+) wherein the cancer cells comprise colorectal cells (column 8, lines 6+). US Patent No. 6,252,050 further teaches that the biological characteristics of the antibodies include a variable or hypervariable domain of the anti-DR5 monoclonal antibody secreted by the hybridoma deposited as ATCC accession No. HB-12534 (column 23, lines 4-21) include exposing said antibodies *in vitro* or *in vivo* (column 23, lines 10+) and that the method further comprises antibodies which bind to the same DR5 receptor epitope to which the anti-DR5 monoclonal secreted by the

hybridoma deposited as ATCC accession No. HB-12534 binds (column 23, lines 4-21 and column 32). The patent further includes expression of the antibody in a recombinant host cell selected from the group consisting of a yeast cell (column 24, line 1). The patent further teaches binding affinities in the range of 10^8 M^{-1} to $10^{12}M^{-1}$ (figures 6A-6C).

2. The patent does not specifically teach co-administration of the antibody with CPT-11.
3. Rougier *et al.* teach the clinical efficacy of CPT-11 in the treatment of colorectal cancer and that CPT-11 would be a welcome addition to the oncology armamentarium for this malignancy.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to optimize the method taught by US Patent No. 6,252,050 by including CPT-11 since both drugs are useful in treating cancer. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of the clinical efficacy of CPT-11, it would have been obvious to induce apoptosis in mammalian cancer cells including colorectal cancer cells with a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11 because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as anti-cancer agents.

Claims 6-13, 19-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/51793, November 1998, IDS, in view of Rougier *et al.* (Semin.Oncol, 1996, Vol. 23, Abstract only).

4. WO 98/51793 teaches a method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of agonistic anti-DR5 receptor antibody (page 50) (The DR5 polypeptide is also known as Apo-2- see page 6 of the specification.) wherein said anti-DR5 receptor antibody is monoclonal, wherein said monoclonal comprises a chimeric antibody or human antibody (page 47, 51); wherein said antibody is an antibody which cross reacts with more than one Apo-2 ligand receptor (page 11, line 10+, page 50); wherein said method further comprises exposing said cancer cells to one or more growth inhibitory substances or radiation (page 60, line 4+) wherein the cancer cells comprise colorectal cells (page 18, line 35+). WO 98/51793 further teaches that the biological characteristics of the antibodies include a variable or hypervariable domain of the anti-DR5 monoclonal antibody secreted by the hybridoma deposited as ATCC accession No. HB-12456 (page 16, line 25+, page 50) include exposing said antibodies *in vitro* or *in vivo* (page 18, line 13) and that the method further comprises antibodies which bind to the same DR5 receptor epitope to which the anti-DR5 monoclonal secreted by the hybridoma deposited as ATCC accession No. HB-12456 binds (page 50). The patent further includes expression of the antibody in a

recombinant host cells including CHO cells (page 49, line 32+). The patent further teaches binding affinities in the range of 10^8 M^{-1} to $10^{12}M^{-1}$ (figure 11).

5. WO 98/51793 does not specifically teach co-administration of the antibody with CPT-11.
6. Rougier *et al.* teach the clinical efficacy of CPT-11 in the treatment of colorectal cancer and that CPT-11 would be a welcome addition to the oncology armamentarium for this malignancy.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to optimize the method taught by WO 98/51793 by including CPT-11 since both drugs are useful in treating cancer. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of the clinical efficacy of CPT-11, it would have been obvious to induce apoptosis in mammalian cancer cells including colorectal cancer cells with a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11 because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as anti-cancer agents.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
November 2, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600